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**(54) PROCESS FOR PRODUCING A HYDROXY APATITE-COATED IMPLANT**

VERFAHREN ZUR HERSTELLUNG EINES MIT HYDROXYLAPATIT ÜBERZOGENEN IMPLANTATS

PROCEDE D'ELABORATION D'UN IMPLANT AYANT UNE COUCHE D'HYDROXYAPATITE

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## Description

[0001] The present invention relates to a method for the production of an implant.

## BACKGROUND ART

[0002] The following methods have been typically known as ways of coating a metallic substrate with hydroxyapatite.

(1) A plasma spraying method using hydroxyapatite as a starting material (see, for example, KOKAI (Japanese Unexamined Patent Publication) No. 58-39533, KOKAI No. 62-34566).

(2) A method comprising the steps of preparing a powder formed mainly of a calcium salt and a phosphorus salt as a starting material, applying a coating film of the powder onto a metallic substrate by the plasma spraying technique, and immersing the coated metallic substrate in an atmosphere of steam or in water thereby converting the powder film into hydroxyapatite (see, for example, KOKAI No. 63-93851).

(3) A method comprising the steps of applying to the surface of a metallic substrate an organic-solvent coating liquid having an organic calcium compound and an organic phosphorus compound dissolved therein and heating and firing the coated metallic substrate thereby forming a hydroxyapatite coating film on the metallic substrate (thermal decomposition method) (see, for example, KOKAI No. 64-86975).

[0003] The method (1) mentioned above which uses hydroxyapatite as the starting material for plasma spraying proceeds through the steps of heating and cooling because of the operating principle of plasma flame spraying and tends to submit the hydroxyapatite to decomposition and, therefore, entails the following problems.

(a) Alkali components such as calcium oxide and tetracalcium phosphate persist as residues in the coating film.

(b) An amorphous phase occurs in the coating film.

(c) Since the alkali components and the amorphous layer mentioned above have high degrees of solubility and the coating layer of hydroxyapatite (HAP) itself succumbs to solution readily, the produced composite poses the problem of betraying deficiency in lasting biostability, yields to embrittlement in the course of solution, possibly suffers from a local increase in pH in a living body, and entails a problem of biocompatibility.

(d) Regarding the HAP layer, since the IR absorption spectrum of the produced composite after separation therefrom of the HAP layer in a crushed

form shows no discernible absorption peak originating in the hydroxyl group, this HAP layer does not deserve to be called a stoichiometric hydroxyapatite and poses the problem of offering no sufficient chemical stability.

[0004] The method (2) mentioned above has the problem of not only rendering it difficult to form a single apatite phase from the calcium salt and phosphorus salt by the solid phase reaction recording to the plasma spraying technique but also submitting the reaction to the onset of decomposition. Even the immersion in an atmosphere of steam or in water lends no impetus to the reaction for conversion into a single hydroxyapatite phase but entails the disadvantage that the formation of calcium carbonate and other substances ensues, the solution advances, and the coating layer embrittles.

[0005] The thermal decomposition method (3) mentioned above, similarly to the plasma spraying method, has the problem of tending to form an amorphous phase of calcium oxide and tetracalcium phosphate and rendering it difficult for the coating layer to be converted into a single phase of stoichiometric hydroxyapatite. And, owing to the fact that the substrate itself is fired in the open air, this method also has the problem of giving rise to an oxide coating layer between the substrate and the HAP coating layer and, depending upon the firing conditions, the oxide coating layer becomes brittle and when the HAP coating layer is completely dissolved in a living body and consequently exposed to the vital tissue, inducing the occurrence of macrophage and foreign giant cells and causing a foreign reaction.

[0006] Besides the methods cited above, methods such as sputtering and chemical vapour disposition are available for the coating of a metallic substrate with hydroxyapatite. These methods, however, have not been technically established as evinced by the fact that they experience great difficulty in obtaining calcium phosphate of high crystallinity.

[0007] EP-A-0285826 discloses the coating of  $\alpha$ - or  $\beta$ -tricalcium phosphate on a titanium substrate by plasma spraying, followed by forming apatite layer by the reaction with water at 80 - 100°C for from 10 days to 6 weeks.

[0008] EP-A-0407698 discloses the formation of the coating layer of hydroxyapatite, etc. on a substrate by plasma spraying, followed by the two step treatments of the rehydration treatment and the pressure sintering treatment (i.e., HIP treatment) to effect the crystallization.

[0009] DE-A-3709457 discloses the production of a titanium composite material coated with a calcium phosphate compound by coating a calcium phosphate solution on the surface of the substrate, followed by sintering the coating layer at 300 - 900°C to form a covering layer of the calcium phosphate compound and further, followed by hydrothermal treatment of the covering layer, if necessary, for 30 minutes to several hours.

[0010] Accordingly, the present invention seeks to provide a method for quick and accurate production of an implant having an apatite type ceramic coating layer formed on the surface of a core material (substrate).

[0011] Other advantages of the present invention will become apparent from the following description.

[0012] In accordance with the present invention, there is provided a method for the production of an implant, consisting essentially of

coating a core material with at least one calcium phosphate compound selected from the group consisting of  $\alpha$ -tricalcium phosphate and  $\beta$ -tricalcium phosphate by plasma spraying to form a coating layer on the core material and; then, converting said coating layer into an apatite ceramic layer by subjecting the coating core material to a hydrothermal treatment in an aqueous solution containing  $\text{Ca}^{2+}$  ions and  $\text{PO}_4^{3-}$  ions at a temperature of from 80°C to 200°C for from 0.5 to 100 hrs.

[0013] In the light of the prior art described above, the present invention has succeeded in perfecting a method for producing an implant having as an outermost layer or coating layer thereof of an accurate and stable stoichiometric hydroxyapatite and apatite type ceramic layer by forming on a core material (substrate) a coating layer of a calcium phosphate type compound by the process of plasma spraying, and then submitting the resultant coated core material to a hydrothermal treatment. In the present invention, the terms "coating" and "coating film" are used synonymously.

[0014] In accordance with the method of production contemplated by the present invention, a calcium phosphate coating layer is first formed on the surface of a core material (substrate) by the process of plasma spraying.

[0015] Then, the coating layer is hydrothermally treated in an aqueous solution simultaneously containing calcium ion and phosphate ion or an aqueous calcium phosphate solution at a temperature in the range of, for example, between 80°C and 200°C for a period of between 0.5 and 100 hours. The material which has undergone this hydrothermal treatment has had the crystal structure thereof transformed into hydroxyapatite, which is confirmed by the X-ray diffraction process to constitute a single hydroxyapatite phase of very high crystallinity and is found by the IR absorption process and the Raman spectroscopy method to have a clear absorption by the hydroxyl group. The coating layer produced in the manner described above is an extremely stable chemical as evinced by the fact that it is substantially equal in solubility in physiological saline solution or simulated humor to a sintered stoichiometric hydroxyapatite article having the same surface area.

[0016] When the calcium phosphate coating layer which has been formed by the process cited above is

subsequently treated hydrothermally in the same manner as described above in a solution simultaneously containing a metallic ion such as an alkali metal ion or alkaline earth metal ion and an anion of carbonic acid, nitric acid, sulfuric acid, boric acid, or halogen ion or in a solution containing any of the above-mentioned ions alone, it is converted into a material of apatite structure containing the relevant ions mentioned above. Thus, a novel implant material conforming to a particular purpose of use can be obtained.

[0017] The term "implant" as used in the present invention refers to substitutes, prosthetics, reinforcements, etc., for such hard vital tissues as artificial roots of teeth, artificial bones, and bone plates, etc.

[0018] The core material (referred to occasionally as "substrate" or "basic plate"), though variable in shape with the kind of implant aimed at, is made of a metallic material such as Ti alloy or stainless steel or ceramic material.

[0019] The calcium phosphate type compounds which are effectively usable in the method of the present invention include, for example,  $\alpha$ - and  $\beta$ -tricalcium phosphates (TCP), octacalcium phosphate, and amorphous calcium phosphate. These calcium phosphate type compounds can be used either alone or in any mixture thereof.

[0020] The "hydrothermal treatment" involved in the method of the present invention refers to a procedure which comprises immersing a calcium phosphate-coated implant material in water such as an aqueous solution simultaneously containing calcium ion and phosphate ion, hermetically sealing the immersed implant material (in an atmosphere of such inert gas as air, nitrogen, or argon gas), and heating the sealed immersed implant material. By this treatment, the coating layer is enabled to be formed of a more stoichiometric hydroxyapatite. The term "stoichiometric hydroxyapatite" as used herein refers to  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ .

[0021] The conditions employed for the hydrothermal treatment and the solution used for the treatment are variable with a particular species of apatite layer aimed at. For the purpose of mainly producing a single hydroxyapatite layer, this hydrothermal treatment is desired to be performed in a solution simultaneously containing calcium ion and phosphate ion or an aqueous calcium phosphate solution or distilled water at a temperature of 200°C or less, preferably falling in the range between 90°C and 150°C, for a period of 100 hours or less, preferably falling in the range between 6 and 72 hours.

[0022] In the present invention, the preparation of the components of the solution for the hydrothermal treatment and the setting of the temperature of treatment and the period of treatment (hereinafter these factors of the hydrothermal treatment may be occasionally referred to collectively as "environment of hydrothermal treatment") are easy to attain. Thus, a varying species

of apatite layer conforming to a particular purpose of use can be produced.

[0023] The apatite type ceramic produced by the method of the present invention is such that the apatite type ceramic layer is allowed to have part of the metallic ions other than Ca and the anions other than  $\text{PO}_4$  or OH (hydroxyl group) substituted by adjusting the components such as of the aqueous solution to be used for the hydrothermal treatment mentioned above. Optionally, the coating layer may be formed of an apatite type ceramic substance (such as, for example, strontium apatite, magnesium apatite, chlorine apatite, fluorine apatite, or carbonate apatite) other than hydroxyapatite.

## EXAMPLES

[0024] The present invention will now be further illustrated by the following Examples.

### Example 1

[0025] A  $\alpha$ -tricalcium phosphate (TCP)-metal composite material was obtained by forming a calcium phosphate coating layer on a metallic substrate (metal: titanium) by the plasma spraying process using TCP powder as the starting material for spraying. The composite material thus obtained was immersed in an aqueous solution simultaneously containing  $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$  ions at a pH value of 9.0 (which may be in the range of a pH of 6 to 12) (or in an aqueous calcium phosphate solution having a pH value in the range of 5.5 to 12.5), hermetically sealed, and subjected to a hydrothermal treatment at a temperature of 120°C (which may be in the range between 80°C and 200°C). The duration of this treatment was 24 hours (generally within 100 hours). This hydrothermal treatment brought about transformation of crystal structure of the TCP layer into a HAP layer. By X-ray powder diffraction and infrared absorption spectrometry it was confirmed that the HAP layer formed a more stoichiometric chemically stable composition.

### Example 2

[0026] A calcium phosphate coating layer was formed on a metallic substrate (metal: titanium) by the thermal decomposition process using a calcium salt and a phosphoric ester. The resultant composite material was fired at 500°C, a temperature not so high as to induce intense oxidation of the metallic substrate, for five hours to effect thorough combustion of existent carbon sources. The composite material thus obtained was immersed in an aqueous solution simultaneously containing  $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$  ions at a pH value of 7.5 (generally pH 6 - 12) (or in an aqueous calcium phosphate solution having a pH value in the range of 5.5 to 12.5), hermetically sealed, and hydrothermally treated at a temperature of 120°C (generally in the range between

80°C and 200°C). The duration of this treatment was 12 hours (generally within 100 hours). By X-ray powder diffraction and infrared absorption spectrometry it was confirmed that the HAP layer in the composite material that underwent this hydrothermal treatment was formed of a more stoichiometric chemically stable composition.

### Example 3

[0027] A TCP-metal composite material was obtained by forming a calcium phosphate coating layer on a metallic substrate (metal: stainless steel) by the plasma spraying process using TCP powder as the starting material for spraying. The composite material thus obtained was subjected to a hydrothermal treatment in a calcium carbonate solution. The temperature of this treatment was 120°C (generally in the range between 80°C and 200°C) and the duration of the treatment was 48 hours (generally within 100 hours). By infrared absorption spectrometry and powder X-ray diffraction it was confirmed that, in consequence of the treatment described above, there was produced a composite material comprising an apatite coating layer having carbonic acid partially substituted at the position of the hydroxyl group of the hydroxyapatite structure and a metallic substrate.

### Example 4

[0028] An  $\alpha$ -TCP sprayed layer-metal composite material was obtained by plasma spraying an  $\alpha$ -TCP or  $\beta$ -TCP powder as the starting material for spraying on a metallic substrate (metal: stainless steel). The composite material thus obtained was immersed in an aqueous solution simultaneously containing  $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$  ions at a pH value of 7.0 (generally in the range between pH 6 and 12) (or in an aqueous calcium phosphate solution having a pH value in the range of 5.5 to 12.5), hermetically sealed, and hydrothermally treated at a temperature of 120°C (generally in the range between 80°C and 200°C). The duration of this treatment was 30 hours (generally within 100 hours). By X-ray powder diffraction and infrared absorption spectrometry it was confirmed that the hydrothermal treatment caused transformation of crystal structure of the  $\alpha$ -TCP layer into a HAP layer having a more stoichiometric chemically stable composition.

[0029] By controlling the duration of the hydrothermal treatment (for example, 1.5 hours at 120°C in an aqueous solution simultaneously containing  $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$  ions at a pH value in the range between pH 6 and 12), there was obtained a composite material having the transformation into the HAP produced only in the surface region of the layer.

### Example 5

[0030] The surface of a Ti base intended for the root

of a tooth was coarsened by sand blasting (or bead blasting or acid treatment) and subjected to plasma spraying using a  $\beta$ -TCP powder having a particle size distribution of 30 to 60  $\mu\text{m}$  to form a coating layer of  $\alpha$ -TCP thereon. In a HAP gel prepared by dissolving in water a HAP synthesized by a wet process, the coated base was immersed in such a manner as to keep the HAP particles from directly contacting the artificial root of a tooth and then subjected to a hydrothermal treatment at 120°C for 30 hours. Consequently, there was obtained a composite material having the coating layer thereof transformed from the  $\alpha$ -TCP layer into a HAP layer (confirmed by X-ray powder diffraction and infrared absorption spectrometry).

[0031] The apatite type ceramic layer to be produced by the hydrothermal treatment is required to be formed at least in the outermost layer. Of course, the coating layer may be wholly formed of the apatite type ceramic substance.

#### INDUSTRIAL APPLICABILITY

[0032] As described above, the method of according to the present invention for the production of an implant enables an apatite type ceramic layer represented by a chemically stable hydroxyapatite layer to be produced without resorting to the process of producing a calcium phosphate coating layer. By varying the environment of hydrothermal treatment, there can be formed an apatite type ceramic layer having part of the metallic ions and anions thereof substituted. Since the transformation of crystal structure is effected very quickly and accurately, the method permits mass production of the implant. The present invention, therefore, provides very high economic utility.

#### Claims

1. A method for the production of an implant, consisting essentially of

coating a core material with at least one calcium phosphate compound selected from  $\alpha$ -tricalcium phosphate and  $\beta$ -tricalcium phosphate by plasma spraying to form a coating layer on the core material and; then, converting said coating layer into an apatite ceramic layer by subjecting the coating core material to a hydrothermal treatment in an aqueous solution containing  $\text{Ca}^{2+}$  ions and  $\text{PO}_4^{3-}$  ions at a temperature of from 80°C to 200°C for from 0.5 to 100 hrs.

2. A method as claimed in claim 1, wherein said core material is a metallic substrate formed of a material selected from titanium, a titanium alloy, stainless steel, a cobalt-chromium alloy, and a nickel-titanium alloy.

3. A method as claimed in claim 1 or claim 2, wherein said hydrothermal treatment is carried out at a pH value of from 6 to 12.

4. A method as claimed in claim 1 or claim 2, wherein said hydrothermal treatment is carried out in an aqueous calcium phosphate solution having a pH value of from 5.5 to 12.5 at a temperature of from 80° to 200°C.

5. A method as claimed in any one of claims 1 to 4, wherein said hydrothermal treatment is carried out for between 6 and 72 hrs.

#### Patentansprüche

1. Verfahren zur Herstellung eines Implantats, das im wesentlichen besteht aus

dem Beschichten eines Kernmaterials mit wenigstens einer Calciumphosphatverbindung, ausgewählt aus  $\alpha$ -Tricalciumphosphat und  $\beta$ -Tricalciumphosphat durch ein Plasmasprühverfahren zur Ausbildung einer Beschichtung auf dem Kernmaterial und anschließend

Umwandeln der Beschichtung in eine Apatitkeramikschiicht, indem das beschichtete Kernmaterial 0,5 bis 100 Stunden lang einer hydrothermalen Behandlung in einer wässrigen Lösung, die  $\text{Ca}^{2+}$ - und  $\text{PO}_4^{3-}$ -Ionen enthält, bei einer Temperatur von 80 bis 200°C unterzogen wird.

2. Verfahren nach Anspruch 1, worin das Kernmaterial ein metallisches Substrat ist, das aus einem Material gebildet wird, welches aus Titan, einer Titanlegierung, rostfreiem Stahl, einer Kobalt/Chrom-Legierung und einer Nickel/Titan-Legierung ausgewählt ist.

3. Verfahren nach Anspruch 1 oder 2, worin die hydrothermale Behandlung bei einem pH-Wert von 6 bis 12 durchgeführt wird.

4. Verfahren nach Anspruch 1 oder 2, worin die hydrothermale Behandlung in einer wässrigen Calciumphosphatlösung mit einem pH-Wert von 5,5 bis 12,5 bei einer Temperatur von 80 bis 200°C durchgeführt wird.

5. Verfahren nach einem der Ansprüche 1 bis 4, worin die hydrothermale Behandlung zwischen 6 und 72 Stunden lang durchgeführt wird.

#### Revendications

1. Procédé pour la production d'un implant, consistant

essentiellement à

revêtir une matière centrale avec au moins un  
phosphate de calcium choisi entre le phos-  
phate tricalcique  $\alpha$  et le phosphate tricalcique  $\beta$  5  
par pulvérisation par plasma pour former une  
couche de revêtement sur la matière centrale ;  
puis  
à transformer ladite couche de revêtement en  
une couche céramique d'apatite en soumettant 10  
la matière centrale revêtue à un traitement  
hydrothermique dans une solution aqueuse  
contenant des ions  $\text{Ca}^{2+}$  et des ions  $\text{PO}_4^{3-}$  à  
une température comprise dans l'intervalle de  
80°C à 200°C pendant un temps de 0,5 à 100 15  
heures.

2. Procédé suivant la revendication 1, dans lequel la  
matière centrale consiste en un substrat métallique  
formé d'une matière choisie entre le titane, un 20  
alliage de titane, l'acier inoxydable, un alliage  
cobalt-chrome et un alliage nickel-titane.
3. Procédé suivant la revendication 1 ou la revendica-  
tion 2, dans lequel le traitement hydrothermique est 25  
effectué à une valeur de pH de 6 à 12.
4. Procédé suivant la revendication 1 ou la revendica-  
tion 2, dans lequel le traitement hydrothermique est 30  
effectué dans une solution aqueuse de phosphate  
de calcium ayant une valeur de pH de 5,5 à 12,5 à  
une température de 80° à 200°C.
5. Procédé suivant l'une quelconque des revendica-  
tions 1 à 4, dans lequel le traitement hydrothermi- 35  
que est effectué pendant un temps de 6 à 72  
heures.

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